Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Fractionation for whole breast irradiation: an American Society for Radiation Oncology (ASTRO) evidence-based guideline.

Bibliographic Source(s)

Smith BD, Bentzen SM, Correa CR, Hahn CA, Hardenbergh PH, Ibbott GS, McCormick B, McQueen JR, Pierce LJ, Powell SN, Recht A, Taghian AG, Vicini FA, White JR, Haffty BG. Fractionation for whole breast irradiation: an American Society for Radiation Oncology (ASTRO) evidence-based guideline. Int J Radiat Oncol Biol Phys. 2011 Sep 1;81(1):59-68. [66 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

The bases of recommendations (U-evidence or U opinion) are defined at the end of the "Major Recommendations" field.

1. Which patients obtain equivalent results from hypofractionated whole breast irradiation (HF-WBI) and conventionally fractionated whole breast irradiation (CF-WBI)?
   Guideline

   Evidence from randomized clinical trials has demonstrated that HF-WBI and CF-WBI are equally effective for in-breast tumor control and comparable in long-term side effects for patients meeting all the criteria listed in the Table 1 (below) (U-evidence). The task force was unable to reach agreement as to the equivalence of HF-WBI to CF-WBI for patients who do not satisfy all these criteria, and thus, they could not make a recommendation either for or against the use of HF-WBI in such patients.

   Table 1. Evidence Supports the Equivalence of Hypofractionated Whole Breast Irradiation with Conventionally Fractionated Whole Breast Irradiation for Patients who Satisfy all of These Criteria*

   1. Patient is 50 years or older at diagnosis
   2. Pathologic stage is T1–2 N0 and patient has been treated with breast-conserving surgery
   3. Patient has not been treated with systemic chemotherapy
   4. Within the breast along the central axis, the minimum dose is no less than 93% and maximum dose is no greater than 107% of the prescription dose (±7%;) (as calculated with 2-dimensional treatment planning without heterogeneity corrections)

*For patients who do not satisfy all of these criteria, the task force could not reach consensus and therefore chose not to render a recommendation either for or against hypofractionated whole breast irradiation in this setting. Please see the text for a thorough discussion of tumor grade. Patients receiving any type of whole breast irradiation should generally be suitable for breast-conserving therapy with regards to standard selection rules (e.g., not pregnant, no evidence of multicentric disease, no prior radiotherapy to the breast, no history of certain collagen-vascular diseases).

2. What is the role of a tumor-bed radiation boost in patients treated with HF-WBI?
   Guideline

   There were few data to define the indications for and toxicity of a tumor bed boost in patients treated with HF-WBI (U-evidence). The task force agreed that the use of HF-WBI alone (without a boost) is not appropriate when a tumor bed boost is thought to be indicated (U-opinion). When a boost is indicated, there was lack of consensus regarding the appropriateness of HF-WBI. Although the majority of the task force members thought that there were sufficient data showing the safety of HF-WBI followed by a tumor bed boost to recommend its use in otherwise suitable patients, a minority believed that CF-WBI should be used instead when a tumor bed boost is indicated.

3. What are appropriate regimens for HF-WBI and a tumor-bed boost?
   Guideline

   For patients not receiving a tumor-bed boost, the task force favored a dose of 42.5 Gy in 16 fractions over approximately 22 days when HF-WBI is planned (U-evidence). The optimal HF-WBI regimen to use when a boost is given and the optimal tumor-bed boost dose-fractionation to use in conjunction with HF-WBI have not been determined (U-evidence).

4. What are the characteristics of an acceptable radiotherapy plan for patients treated with HF-WBI?
   Guideline

   Two-dimensional treatment planning with optimization of dose homogeneity in the central axis is the minimum acceptable standard for HF-WBI treatment planning (U-evidence). However, CT-guided treatment planning using three-dimensional dose compensation is strongly recommended to optimize dose homogeneity throughout the entire breast (U-opinion). As a conservative measure, the task force recommended exclusion of the heart from the primary treatment fields provided that coverage of the primary tumor site is not compromised (U-opinion).

5. What insights relevant to the radiobiology of breast cancer can be gained from recently published clinical trials comparing CF-WBI with HF-WBI?
   Guideline

   The randomized trials comparing CF-WBI with HF-WBI have suggested that the extent of both local control of subclinical breast cancer and late change in breast appearance exhibit similar sensitivity to fraction size as modeled by the α/β ratio in the linear-quadratic (LQ) formulation (U-evidence). Additional clinical data are needed to quantify the effects of overall treatment time, dose homogeneity, and systemic agents on tumor control and normal tissue toxicity (U-evidence) (see Table 7 in the original guideline document).

Definitions:

Bases of Recommendations

Unanimous recommendations based firmly on evidence are specified with a "(U-evidence)" and unanimous recommendations based on expert opinion are specified with a "(U-opinion)."

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Early-stage breast cancer

Guideline Category

Treatment

Clinical Specialty

Obstetrics and Gynecology

Oncology

Radiation Oncology

Radiology

Intended Users

Patients

Physicians

Guideline Objective(s)

- To provide clinically useful evidence-based guidelines on whole breast irradiation (WBI) fractionation to provide direction for clinical practice
- To help radiation oncologists and breast cancer patients determine the appropriate use of hypofractionated (HF)-WBI as adjuvant treatment for breast cancer following breast-conserving surgery

Target Population

Women who have undergone breast-conserving surgery for early-stage breast cancer

Interventions and Practices Considered

1. Hypofractionated whole breast irradiation (HF-WBI)
2. Conventionally fractionated whole breast irradiation (CF-WBI)
3. Radiotherapy treatment plan
    - Two-dimensional with optimization of dose homogeneity
    - Computed tomography (CT)-guided with three-dimensional dose compensation

Major Outcomes Considered

- Tumor control (local control, local-regional control, disease-free survival, overall survival)
- Toxicity (cosmesis, skin, soft tissue, pulmonary, cardiac, brachial plexus, rib) endpoints

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

For the purposes of this literature review, the task force defined hypofractionated (HF) as a daily dose exceeding 2 Gy and conventionally fractionated (CF) as a daily dose of 2 Gy or less. Whole breast irradiation (WBI) was defined as radiation intended to treat all clinically detectable breast tissue ipsilateral to the index cancer. Studies pertinent to the guideline topic were identified by searching the National Library of Medicine's PubMed database for articles published from January 1, 1990, through February 28, 2009. For the initial screen, the task force selected English-language studies categorized under the Medical Subject Heading (MeSH) "Breast neoplasms/radiotherapy" with any of the following key words: hypofractionation, hypofractionated, fractionation, fraction, accelerated, short, or shorter. Of 558 candidate abstracts screened, the task force sought to identify randomized trials that compared HF-WBI with other treatments and also nonrandomized clinical studies with the primary purpose of evaluating any aspect of HF-WBI. The task force identified six randomized clinical trials that compared HF-WBI with CF-WBI: Hôpital Necker, Queen Elizabeth, Canadian, Royal Marsden Hospital/Gloucester Oncology Center (RMH/GOC), and Standardization of Breast Radiotherapy (START) A and B. The task force also identified two randomized clinical trials that compared HF-WBI with partial breast irradiation (PBI), two randomized clinical trials that compared HF-WBI with no irradiation, and one randomized trial that compared HF-WBI alone with HF-WBI followed by a boost to the tumor bed. Additionally, 34 nonrandomized clinical studies met inclusion criteria (see www.redjournal.org, Table e1 [see appendices in the "Availability of Companion Documents" field). Articles in which the sole focus was postmastectomy radiation or concurrent chemoradiation were excluded. Bibliographies of candidate articles were also reviewed to ensure that all relevant articles were included. Studies published in abstract form only were not included, with the exception of the updated results of the Canadian trial presented at the 2008 American Society for Radiation Oncology Annual Meeting (the manuscript corresponding to this abstract was published on February 11, 2010, and was also included in final deliberations of this guideline).

Number of Source Documents

The task force identified six randomized clinical trials that compared hypofractionated whole breast radiation (HF-WBI) with conventionally-fractionated whole breast radiation (CF-WBI), two randomized clinical trials that compared HF-WBI with partial breast irradiation (PBI), two randomized clinical trials that compared HF-WBI with no irradiation, and one randomized trial that compared HF-WBI alone with HF-WBI followed by a boost to the tumor bed. Additionally, 34 nonrandomized clinical studies met inclusion criteria.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Not Given)

Rating Scheme for the Strength of the Evidence

Not stated

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

On the basis of results of the systematic literature review, evidence tables were constructed to summarize tumor control (local control, local-regional control, disease-free survival, overall survival) and toxicity (cosmesis, skin, soft tissue, pulmonary, cardiac, brachial plexus, rib) endpoints.

The quality of randomized clinical trials was evaluated using criteria adapted from the United States Preventive Services Task Force Procedure Manual. The Queen Elizabeth trial reported psychological outcomes only and thus was not included in the evidence tables or formally scored for quality.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The American Society for Radiation Oncology (ASTRO) Health Services Research Committee (HSRC) convened a task force to formulate clinically useful evidence-based guidelines on whole breast irradiation (WBI) fractionation. The task force conducted a systematic review of the literature, which, supplemented by the expertise and clinical experience of the task force members, provided the rationale for the recommendations.

The task force included eight recognized experts in breast cancer radiation oncology, one in radiobiology, one in radiation physics, two representatives from the HSRC, one radiation oncologist in private practice, one radiation oncology resident, and one patient advocate. The task force was charged with using currently available evidence to develop a clinically practical, evidence-based guideline to help radiation oncologists and breast cancer patients determine the appropriate use of HF-WBI as adjuvant treatment for breast cancer following breast-conserving surgery.

Through a series of conference calls, the task force completed the systematic literature review, reviewed evidence tables, and formulated the guidelines contained herein.

During the formulation of this evidence-based guideline, the task force sought to adhere to the American Medical Association's Physician Consortium for Performance Improvement guidance for measure development and recent calls for reform of the guideline process. It was noted that although this guideline strives to be firmly evidence-based, the opinions of the individual task force members inevitably inform their interpretation and application of the available evidence. As a result, it has been recommended that guidelines include "alternate interpretations and viewpoints" along with the majority opinion to ensure that the final guideline is representative of all task force members' input. In this guideline, unanimous recommendations based firmly on evidence are specified with a "(U-evidence)" and unanimous recommendations based on expert opinion are specified with a "(U-opinion)." When unanimity could not be reached, majority and minority opinions are presented and specified.

Rating Scheme for the Strength of the Recommendations

Unanimous recommendations based firmly on evidence are specified with a "(U-evidence)" and unanimous recommendations based on expert opinion are specified with a "(U-opinion)."

Cost Analysis

Widespread adoption of hypofractionated whole breast irradiation (HF-WBI) for appropriately selected patients has the potential to enhance the convenience of treatment and lower the costs of whole breast irradiation (WBI).

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The initial draft of the manuscript was reviewed by five expert reviewers and American Society for Radiation Oncology (ASTRO) legal counsel and was subsequently placed on the ASTRO Web site in January 2010 for a 3-week period of public comment. Following integration of all feedback, the document was submitted to the *International Journal of Radiation Oncology, Biology, and Physics* for additional peer review and, finally, to the ASTRO Board of Directors for their review and approval in May 2010.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate treatment with hypofractionated whole breast irradiation (HF-WBI) or conventionally fractionated whole breast irradiation (CF-WBI) in patients with early stage breast cancer

Potential Harms

- Toxicity associated with hypofractionated whole breast irradiation (HF-WBI) and conventionally fractionated whole breast irradiation (CF-WBI) (see Table 6 of the original guideline document for details)
- Collectively, one "fair" and three "good" randomized trials demonstrated that several HF-WBI regimens produced ipsilateral breast tumor recurrence (IBTR) rates and toxicity profiles comparable with those for CF-WBI (50 Gy in 25 fractions). In addition, two randomized clinical trials that compared HF-WBI with partial breast irradiation (PBI) and two randomized clinical trials that compared HF-WBI with no irradiation demonstrated a lower risk of IBTR with HF-WBI than with regimens in the other arms of these trials.
- There is limited evidence from prospective randomized trials to define the toxicity and efficacy of a tumor bed boost in patients treated with HF-WBI.

Qualifying Statements

Qualifying Statements

- Adherence to the recommendations set forth in this Guideline will not ensure successful treatment in every situation. Furthermore this Guideline should not be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient.
- American Society for Radiation Oncology assumes no liability for the information, conclusions, and findings contained in its evidence-based guidelines. In addition, these guidelines cannot be assumed to apply to the use of these interventions performed in the context of clinical trials, given that clinical studies are designed to evaluate or validate innovative approaches in a disease for which improved staging and treatment are needed or are being explored.
- It is important to note that this guideline should not be interpreted to prohibit or oppose the use of hypofractionated whole breast irradiation (HF-WBI) for patients not meeting all the criteria listed in Table 1 (see the "Major Recommendations" field) but rather that the evidence was not sufficient to reach consensus for such patients. Many task force members use HF-WBI for many such patients, although their own patterns of practice often differ substantially from one another.
- The task force would also emphasize that although the evidence reviewed and expert opinion generated in the development of this guideline support the noninferiority of HF-WBI compared to conventionally fractionated whole breast irradiation (CF-WBI) for selected patients with early-stage breast cancer, the largest body of data demonstrating the safety, effectiveness, and long-term toxicities of breast-conserving therapy comes from trials and retrospective studies using CF-WBI. Therefore, for patients who do not meet the criteria set forth in Table 1 (see the "Major Recommendations" field), as well as for those patients who do meet these criteria, patients and their treating physicians may prefer CF-WBI on the basis of the abundance of long-term data.

Implementation of the Guideline

Description of Implementation Strategy

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Foreign Language Translations

Patient Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

IOM Domain

Effectiveness

Patient-centeredness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Smith BD, Bentzen SM, Correa CR, Hahn CA, Hardenbergh PH, Ibbott GS, McCormick B, McQueen JR, Pierce LJ, Powell SN, Recht A, Taghian AG, Vicini FA, White JR, Haffty BG. Fractionation for whole breast irradiation: an American Society for Radiation Oncology (ASTRO) evidence-based guideline. Int J Radiat Oncol Biol Phys. 2011 Sep 1;81(1):59-68. [66 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Sep 1

Guideline Developer(s)

American Society for Radiation Oncology - Professional Association

Source(s) of Funding

American Society for Radiation Oncology

Guideline Committee

American Society for Radiation Oncology (ASTRO) Task Force

Composition of Group That Authored the Guideline

Task Force Members: Benjamin D. Smith, M.D., Department of Radiation Oncology, University of Texas M. D. Anderson Cancer Center, Houston; Soren M. Bentzen, Ph.D., D.Sc., Department of Human Oncology, University of Wisconsin School of Medicine and Public Health, Madison, WI; Candace R. Correa, M.D., Department of Radiation Oncology, University of Michigan, Ann Arbor, MI; Carol A. Hahn, M.D., Department of Radiation Oncology, Duke University Medical Center, Durham, NC; Patricia H. Hardenbergh, M.D., Shaw Regional Cancer Center, Vail, CO; Geoffrey S. Ibbott, Ph.D., Department of Radiation Physics, University of Texas M. D. Anderson Cancer Center, Houston, TX; Beryl McCormick, M.D., FACR., Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY; Julie R. McQueen, CHES., RHEd., Oncology Patient Navigator, Duke Raleigh Cancer Center, Durham, NC; Lori J. Pierce, M.D., Department of Radiation Oncology, University of Michigan, Ann Arbor; Simon N. Powell, M.D., PH.D., Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY; Abram Recht, M.D., Department of Radiation Oncology, Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, MA; Alphonse G. Taghian, M.D., Ph.D., Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA; Frank A. Vicini, M.D., FACR., Department of Radiation Oncology, Beaumont Cancer Institute, Royal Oak, MI; Julia R. White, M.D., Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, WI; and Bruce G. Haffty, M.D., Department of Radiation Oncology, Cancer Institute of New Jersey, New Brunswick, NJ

Financial Disclosures/Conflicts of Interest

Prior to initiation of this guideline, all members of the Task Force writing the Guideline were required to complete Conflict of Interest statements. These statements are maintained at American Society for Radiation Oncology (ASTRO) Headquarters in Fairfax, VA and pertinent conflict information is published with the report. Individuals with disqualifying conflicts have been recused from participation in this Consensus Statement (please see www.redjournal.org, Appendix eI [see the "Availability of Companion Documents" field], for comprehensive disclaimers and notifications).

Conflicts of interest: none

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the International Journal of Radiation Oncology, Biology, Physics Web site.

Availability of Companion Documents

The following is available:

- Fractionation for whole breast irradiation: an American Society for Radiation Oncology (ASTRO) evidence-based guideline. Appendices. Electronic copies: Available from the International Journal of Radiation Oncology, Biology, Physics Web site.

Patient Resources

The following is available:

- Radiation therapy for breast cancer. Brochure. Fairfax (VA): American Society for Radiation Oncology; 2011. 2 p. Electronic copies: Available from the RT Answers Web site . Also available in Spanish from the RT Answers Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on July 24, 2012. The information was verified by the guideline developer on August 22, 2012.

Copyright Statement

Disclaimer

NGC Disclaimer